SOLUTE MODEL OR CELLULAR ENERGY MODEL?: PRACTICAL AND THEORETICAL ASPECTS OF THIRST DURING EXERCISE

PRESENTED BY

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INTRODUCTION

Most physiologists would agree that repaying the water debt incurred through evaporative cooling is part of the physiological cost of work in the heat. Pitts and coworkers (44) emphasized that, during work in the heat, men never voluntarily drink as much water as they lose and usually replace only two-thirds of the net water loss. Rothstein et al. (52) observed that this occurred even when water was available, and called this phenomenon "voluntary dehydration". Some physiologists feel that voluntary dehydration occurs because "thirst is an inadequate stimulus to drinking" (29). On the other hand, Vokes (58) contends "one of the best examples of a perfectly functioning homeostatic system is water balance". One of our goals is to reconcile the fact that under certain conditions, both of these statements are correct. We will also try to switch the readers interest from water to salt for, although man may drink, "water cannot be held until the missing osmoles are made good" (29). This may be seen as at least one explanation of why "thirst is inadequate" and there are others.

Common sense would dictate that it is quite useless to estimate a "normal" fluid intake because we are dealing with a homeostatic system designed to equate water requirements with the various losses (respiratory, urinary, skin and sweat). Let us look briefly at these as a partial inventory of our water demand. Under normal conditions, respiratory water loss is about 200 ml per day but may be around 350 ml per day for men working in a dry climate and approach 1500 ml per day for men working at altitude in cold air (29). The insensible perspiration may be as low as 500 ml in a moist climate and with a minimum urine volume (<300 ml/day), a person can barely meet obligate losses on 1000 ml of water per day. The obligate urine volume varies with the diet and is high on a high protein diet and low on a carbohydrate diet. A more reasonable figure for urine volume represents a maximum of 1.4 osmoles of metabolic end-products (mostly

urea and surplus electrolytes) per liter of urine on a mixed European-style diet. Thus, the greatest rate of water loss, by far, is represented in a healthy individual by eccrine sweating which most physiologists would agree can be sustained at something over one liter per hour. This makes sense because the maximum rate of gastric emptying has been estimated between 15 to 20 ml/min or 900 to 1200 ml/h (14).

According to Ladell (29), "thirst is primarily a sensation, which often serves as a drive to drink, but the drive and the sensations are not necessarily identical". Ladell (29) has further introduced a concept of "free circulating water" equivalent to some 2 liters which does not appear to participate in the osmotic balance of the body. This suggests that the "drive" to drink would not come into play until this "free circulating water" had been expended. This interesting notion actually delivers two important ideas: (1) There is an inherent "delay" in the onset or drive of thirst. If this could be explained it would then be more accurate to describe thirst as "delayed" rather than "inadequate". and (2) The delay is a manifestation of the body's osmotic control.

Hypertonicity, ADH Release and Thirst

Although the solute composition of the extracellular compartment is markedly different from the intracellular space, the total osmolality (solute concentration not content) is very similar (13). This is because most cell membranes are freely permeable to water. Thus, one can approximate intracellular fluid osmolality by measuring the plasma osmolality (17). The major intracellular osmotic solutes are potassium, magnesium, organic phosphates and protein. The major osmotic solutes in extracellular fluid are normally sodium and its anions, chloride and bicarbonate. They are referred to as impermeant but are kept on the proper side of the membrane by molecular size,

electrical charge or active pumps. Net movement of water is determined by the osmolalities of the intra- and extracellular compartments (43).

The osmolal concentration or osmolality (usually in milliosmoles/kg water) is an indiscriminating summation of all the particles, ions and molecules present in a solution. It is usually measured by freezing point depression or change in vapor pressure. Measured osmolality should be differentiated from effective osmolality, i.e. the concentration of solutes that will create an osmotic force in vivo. For example, sodium is the major determinant of the effective osmolality of the extracellular fluid because its concentration is high and acts as if restricted from entering cells (23). In contrast, urea permeates cells freely and will not exert an osmotic force if elevated in either compartment. The addition of an impermeant solute to the extracellular space causes a net intracellular fluid volume depletion and creates, by definition, a hypertonic state (17). Freezing point depression does not distinguish between permeant and impermeant solutes by measuring osmolality. Thus an elevated plasma osmolality must be checked by calculation of tonicity before it is interpreted as hypertonicity. For example, 2X P Na (mEq/L) + P glucose (mg/dL/18) = approx. tonicity.

Normally intracellular fluid contains about 2/3 of total body solute and 1/3 is in the extracellular fluid. Since water distributes according to the amount of impermeant solute in each compartment, the intracellular fluid contains 2/3 of total body water (TBW) and extracellular fluid 1/3 of TBW. Let us assume for ease of calculation, that the average 70-kg adult is 60% water (TBW=42 L) and 2/3 (28 L) is intracellular and 1/3 (14 L) is extracellular (3.5 L of plasma and 10.5 L of interstitial fluid). Note by calculation (17) that the intravascular or plasma volume is equivalent to 1/12 of the total body water (3.5:42 as 1:12) and that the plasma volume is 1/4 the extracellular volume (3.5:14 as 1:4). Thus, by definition, if a pure water loss occurs (no salt loss),

2/3 comes from the intracellular water, 1/3 from the extracellular water and 1/12 from the intravascular water. In practice, less than 1/12 of the water loss usually comes from the plasma space because of its' increased plasma protein oncotic pressure (17). It also follows that if the extracellular space losses 4 L of isotonic saline, 3/4 would come from the interstitial fluid and 1/4 from the plasma fluid.

In 1937, Gilman (19) demonstrated that intravenous infusions of hyperosmotic sodium chloride would elicit drinking but equally hyperosmotic solutions of urea stimulated thirst poorly. Since urea could diffuse into cells but sodium would produce shrinkage, an osmotic basis for thirst was established. Other solutes which cause withdrawal of water from cells such as sucrose and sorbital were equally effective in producing thirst when infused intravenously (25,26). These observations reenforced the important role of cellular dehydration in triggering thirst and drinking behavior. The classic work of Verney (57) demonstrated that water diuresis in dogs could be inhibited by intracarotid infusions of hypertonic sodium chloride and, therefore, both thirst and antidiuresis were linked to the osmotic withdrawal of water from cells. Verney deduced that the inhibition of water diuresis resulted from neurohypophyseal secretion of vasopressin which later work has confirmed (61). According to Andersson (4), the most potent stimulators of ADH release and thirst are absolute and relative dehydration. Although ADH is released as a function of body osmolality (47,48), it is equally well correlated with plasma sodium (39).

Andersson (5) suggests that sodium, itself, is the crucial factor in the osmotic control of water balance and has proposed that the centrally located osmoreceptors are responding to specific changes in the CSF sodium concentration subsequent to perturbations in the extracellular fluid osmolality. This was supported by the observation that hypertonic sucrose did not stimulate thirst and ADH when infused into the third ventricle (38). Intracerebral infusions of hypertonic sucrose

can inhibit ADH release by dilution-reduction of CSF sodium concentration which argues against a receptor location outside of the blood-brain barrier. Andersson (5) recognizes that there is the possibility that both elevated sodium and cellular dehydration trigger a biochemical process involved in the receptor-excitation mechanism. Andersson (5) has further suggested that angiotensin II might be an activator of a cationic transporting enzyme. Angiotensin II (22), L-norepinephrine (15) and PGE1 (32) interact with sodium, possibly at the level of Na-K-ATPase, in stimulating ADH and thirst.

The ADH of humans and most other mammals is arginine vasopressin produced by the neurohypophysis. Under physiological conditions, ADH release is apparently controled primarily by plasma osmolality but the osmoregulatory system appears to display large individual (46,49) differences (biological variability?) in both sensitivity and threshold. However, this could be analogous to the apparent diferences in the onset of sweating which depends on an acclimation response to repeated exposures. Within any one individual, the plasma vasopressin response (ADH release) is linearly related to plasma osmolality across the same range within which thirst is stimulated (49). Generally, the range of body fluid osmolality in health is between 280-295 mOsm/kg of water or 287$\pm$2% (17). At a plasma osmolality of 280 mOsm/kg water, ADH release is completely inhibited (17) and the urine osmolality is minimal (<100 mOsm/kg of water).

According to Robertson et al (50), the full range of urinary concentrations can be achieved by changing the plasma ADH concentration between 0.5-5.0 pg/ml. The most important action of ADH is to conserve body water by increasing the renal reabsorption of solute-free water which increases urine concentration and decreases flow. Although there is wide variation in the individual thirst threshold, Vokes (58) estimates its average value at 295 mOsm/kg of water. Thus,

at the thirst threshold (the highest plasma osmolality that occurs normally) the increased ADH concentration elicits maximum urinary concentration (UOsm>800-1000 mOsm/kg of water).

According to Feig and McCurdy (17), the mathematical relation between variables across this physiologic range can be expressed by the equations:

$$(0.34)\ X\ (\text{change in } P_{Osm}) = \text{change in plasma ADH in pg/ml}$$

and

$$\text{change in } U_{Osm} = (95)\ X\ (\text{change in } P_{Osm})$$

Thus, a 1 mOsm plasma change increases urine osmolality by almost 100 mOsm and, at the thirst threshold (295 mOsm/kg of water), urine volume is reduced 10 to 20 fold. Therefore, it can be appreciated that ADH and thirst play key roles in maintaining water balance primarily by regulating the plasma osmolality over a very narrow range (59) bounded on the lower end by the osmotic threshold for ADH release (280 mOsm/kg) and on the upper end by the osmotic threshold for thirst (295 mOsm/kg). This lack of complete parity between an increase in osmolality and the behavior of thirst (1. Seeking water, 2. drinking water, 3. ceasing to drink and 4. absorption and distribution; (1)) could represent an important adaptation freeing the animal from "the bother of repeated thirst or drinking bouts in response to minor increases in osmolality" (55). Thus, thirst does not become prominent until the osmotic dehydration exceeds the renal capacity to deal with it physiologically.

EXAMPLE 1
"FREE CIRCULATING WATER"

Ladell (29) has introduced this idea of "free circulating water" which is equivalent to some 2 liters of total body water (TBW) but does not appear to participate in the body's osmotic balance. Let us examine this in light of the current mechanism for thirst stimulation. If we assume that a pure water deficit does not alter the total body solute, then hypertonicity will be proportional to the volume of water lost (17):

$$(\text{normal TBW}) \times (\text{normal } P_{Osm}) = (\text{present TBW}) \times (\text{present } P_{Osm})$$

We will also assume parity between a L and kg of water: If a man begins to lose pure water at normally the lowest plasma osmolality (17) of 280 mOsm/kg water (fully hydrated), we can calculate about how much water will be lost before the average threshold (58) for thirst is reached at 295 mOsm/kg water:

$$(\text{normal TBW}) \times (\text{normal } P_{Osm}) = (\text{thirst TBW}) \times (\text{thirst } P_{Osm})$$

$$(42\ \text{L}) \times (280\ \text{mOsm/kg}) = (?\ \text{L}) \times (295\ \text{mOsm/kg})$$

$$(11{,}760\ \text{mOsm}/295\ \text{mOsm/kg}) = (?\ \text{L}) = 39.9\text{L} = \text{TBW at the thirst threshold}$$

$$(42\ \text{L} - 39.9\ \text{L}) = 2.1\ \text{L} = \text{TBW deficit}$$

This calculation suggests that, on average, 2.1 L of water would be lost before reaching the thirst threshold. This assumes that one begins losing water fully hydrated which is a more common practice in research than other activities. This figure appears to confirm the prior observation by Ladell (29) that there is "**free circulating water**" equivalent to some 2 liters which **does not appear** to participate in the osmotic balance of the body. This calculation provides further support to the two arguments: 1) that thirst is "delayed" rather than "inadequate" and 2) that the delay is a manifestation of the body's osmotic control.

EXAMPLE 2
PURE WATER DEFICIT IN THE HYDRATED STATE: IMPACT ON REHYDRATION

Let us now examine the impact of the thirst threshold on rehydration in a common situation (TBW loss = 6% of body weight or 4.2L; begin fully hydrated).

DEHYDRATION:

First, let us calculate how high the plasma osmolality would be driven without fluid intake.

(normal TBW) X (normal P_{Osm}) = (dehydrated TBW) X (dehydrated P_{Osm})

(42 L) X (280 mOsm/kg) = (42 L- 4.2 L) X (? mOsm/kg)

(11,760 mOsm/37.8 L) = 311.1 mOsm/kg = dehydrated P_{Osm}

In losing 4.2 L of water, the plasma osmolality will rise to 311 mOsm/kg water or 16 mOsm/kg of water above the thirst threshold (295 mOsm/kg of water). At this point, the plasma volume would have contributed (4200 ml/12) about 350 ml of this deficit or was reduced (350 X 100/3500 ml) by 10%. How much fluid would be consumed in returning the plasma osmolality to the thirst threshold (rehydration)?

(dehydrated TBW) X (dehydrated P_{Osm}) = (thirst TBW) X (thirst P_{Osm})

(37.8 L) X (311.1 mOsm/kg) = (295 mOsm/kg) X (? L)

(11,760 mOsm/295 mOsm/kg) = 39.9 L = rehydrated TBW

Thus, at the thirst threshold (a plasma osmolality of 295 mOsm/kg), a TBW of 39.9 L was achieved. Since the prior, dehydrated TBW was 37.8 L, there was a net gain in TBW of 2.1 L (39.9 L - 37.8 L). This suggests that only **50%** (2.1 L X 100/4.2 L) of the fluid deficit will be **rehydrated** before the thirst threshold is reached. Under these conditions, thirst is not "inadequate". The rehydration deficit is an inherent feature of the "offset" between the thirst "set point" relative to the renal diuresis "set point" in the fully hydrated condition. For example, it is not uncommon to assess a fully hydrated condition by having test subjects consume water until

urine specific gravity declines to some target end-point. Thus, fully hydrated test subjects will almost certainly never fully rehydrate. This calculation appears to confirm the early assertion of Pitts and coworkers (44) that subjects rarely consume sufficient water to replace the deficit. Since only 1/12 of this deficit (2.1 L/12 = 175 ml) will come from plasma (3.5 L:42 L as 1:12), or less given its high oncotic pressure, there is very little impact on cardiovascular performance.

EXAMPLE 3
PURE WATER DEFICIT PRODUCING CLINICAL SHOCK

Clinical shock from pure water loss generally requires a sodium above 170 mEq/l (17). This water deficit can be calculated using the following formula (64):

Water deficit (L)=TBW or (0.6 X wt in kg)-[(TBW)X(desired P_{Na})/(measured P_{Na})]

Water deficit = 42L - [(42L)X(140 mEq/L)/(170 mEq/L)]= 42L - 34.6 L = 7.4 L

Thus, in a pure water deficit sufficient to produce shock, one might estimate a minimum loss of some 7.4 L. Since 1/12 of this deficit is coming from the plasma (7400 ml/12 = 616 ml), there is a decline in plasma volume of about 18% (616 ml X 100/3500 ml). One rarely sees a pure water deficit since salt is usually lost as well. The percent body weight loss in this example is 10.6%.

EXAMPLE 4
PURE WATER DEFICIT IN THE HYPOHYDRATED STATE: IMPACT ON REHYDRATION

DEHYDRATION:

If the subjects begin losing water hypohydrated at the thirst threshold with a thirst plasma osmolality of 295 mOsm/kg water (thirst TBW = 39.9 L) and then lose 4.2 L (6% of initial body weight), their plasma osmolality will rise to:

(thirst TBW) X (thirst P_{Osm}) = (dehydrated TBW) X (dehydrated P_{Osm})

(295 mOsm/kg) X (39.9 L) = (39.9 L - 4.2 L) X (? mOsm/kg)

(11,770 mOsm/35.7 L) = 330 mOsm/kg water

total deficit= 6.3 L; plasma deficit (6300 ml/12)= 525 ml;

% change in plasma volume (525 X 100/3500 ml)= 15%

The dehydrated plasma osmolality is 330 mOm/kg and the dehydrated TBW is 35.7 L. If they drink until the starting thirst threshold is reached (rehydrate), they should consume:

REHYDRATION:

(dehydrated TBW) X (dehydrated P_{Osm}) = (thirst TBW) X (thirst P_{Osm})

(35.7 L) X (330 mOsm/kg) = (? L) X (295 mOsm/kg)

(11,781 mOsm/295 mOsm/kg) = 39.9 L (thirst TBW)

Thus, at the thirst threshold (a plasma osmolality of 295 mOsm/kg), a TBW of 39.9 L was achieved. Since the dehydrated TBW was 35.7 L, an intake of 4.2 L was required to reach the thirst threshold. This suggests that, by beginning the dehydration in the hypohydrated state at the thirst threshold, a nearly **100% rehydration** of the dehydration deficit but only 66.7% of the total deficit (6.3 L) could be expected. Therefore, rehydration results will depend upon whether test subjects show up hydrated (50% rehydration) or hypohydrated (100% rehydration) for an experiment producing a 6% loss in body weight as body water.

EXAMPLE 5
HYPOTONIC WATER DEFICIT IN THE HYDRATED, NON-HEAT ACCLIMATIZED STATE

Assume that the subject is unacclimatized to heat and produces a hypotonic sweat (0.43% NaCl = 1/2 isotonic saline) as the source of body water deficit. He begins work in the heat fully-hydrated, normal condition (plasma osmolality = 280 mOsm/kg of water) and then loses 6% of body weight (4.2L) as sweat.

SOLUTE DEFICIT:

We first compute the impact of the solute loss (sweat NaCl) on the total solute content of the body:

The total mOsmoles will be reduced from 11,760 mOsmoles (280mOsm/kg X 42 L) by an amount equivalent to the solute content of the lost sweat. Assume that 1/2 isotonic saline is equivalent to an osmolality of 140 mOsm/kg (0.5 X 280 mOsm/kg), then:

(140 mOsm/kg sweat) X (4.2 L) = **588 mOsmoles of lost solute.**

The new "salt depleted total solute content is11,172 mOsm (11,760 mOsm - 588 mOsm).

DEHYDRATION:

The new "salt-depleted" TBW is now 37.8 L (42.0L - 4.2L). The new "salt-depleted, dehydrated" plasma osmolality would be 295.6 mOsm/kg (11,172 mOsmoles/37.8L). Assume 1/2 of the fluid loss is pure water (2.1L) and the other 1/2 is isotonic saline. The plasma will contribute1/12 of the pure water deficit or 175 ml. The extracellular space would lose 2.1 L of isotonic saline of which the **plasma contributes** (3.5:14 as1:4) 2100 ml X 1/4= 525 ml. If we add the 175 ml from the pure water portion (525 ml + 175 ml = **700ml**), we see that the plasma has

lost **20%** of its volume (700ml X 100/3500 ml) which, as seen above is close to the shock threshold. **Thus a 4.2 L sweat loss has as much impact on the plasma volume (-20%) as a much greater volume (7.4 L) of pure water loss (-18%).**

REHYDRATION:

If the subject now drank pure water until the plasma osmolality reached the thirst threshold (295 mOsm/kg), he would reach a thirst TBW of:

$$(\text{dehydrated TBW}) \times (\text{dehydrated } P_{Osm}) = (\text{thirst TBW}) \times (\text{thirst } P_{Osm})$$

Assume the dehydrated condition to be a TBW of 37.8 L and a salt-depleted, dehydrated plasma osmolality of 295.6 mOsm/kg of water. Assume the plasma osmolality to be 295 mOsm/kg at the thirst threshold.

$$(37.8 \text{ L}) \times (295.6 \text{ mOsm/kg}) = (? \text{ L}) \times (295 \text{ mOsm/kg})$$

$$(11{,}172 \text{ mOsmoles}/295 \text{ mOsm/kg}) = 37.87 \text{ L of TBW}$$

The subject would increase his TBW by only 70 ml (37.87 L - 37.8 L) before the thirst threshold was reached. This is equivalent to only **1.7%** of the initial water deficit (70ml X100/ 4,200 ml). **In contrast to a similar volume of pure water loss from a hydrated starting point, a hypotonic deficit reduces the expected percent rehydration from 50% to 1.7%** This example serves to indicate the impact of solute loss on rehydration. Under these conditions, thirst is not inadequate. The problem is the missing solute. Any fluid intake under these conditions would probably be stimulated by the volume deficit.

EXAMPLE 6
HYPOTONIC WATER DEFICIT IN THE HYDRATED, HEAT ACCLIMATIZED STATE

Assume the subject was producing sweat of minimum sodium concentratration (**a very hypotonic sweat**; 0.17% NaCl = 0.2 isotonic saline) due to heat acclimation and a low salt diet (high aldosterone levels). He subsequently losses 6% of his body weight (4.2L) after beginning work in the heat, **fully hydrated**, then:

SOLUTE DEFICIT:

His total solute content is 280 mOsm/kg X 42L = 11,760 mOsm/kg and his solute loss is equivalent to the sweat solute concentration (280 mOsm/kg X 0.2 = 56 mOsm/kg) X sweat volume (4.2L) = 235 mOsmoles. His salt depleted total solute content is 11,760 mOsmoles - 235 mOsmoles =11,525 mOsmoles.

DEHYDRATION:

His salt-depleted, dehydrated TBW is 37.8 L and, therefore, the plasma osmolality would be: 11,525 mOsm/37.8 L = 305 mOsm/kg of water. This deficit is equivalent to 839 ml (1000 ml X 235/280) of isotonic saline or 0.84 L saline. The plasma contributes 25% or 210 ml of this deficit (839 ml/4). The remaining deficit is pure water (4200 ml - 839 ml = 3361 ml) of which the **plasma contributes** 1/12 or 280ml. The total plasma deficit is 490 ml (280 ml + 210 ml) or **14%** (490 ml X 100/3500 ml) of the plasma volume.

REHYDRATION:

If the subject drank until the plasma osmolality reached the thirst threshold, then:

(dehydrated TBW) X (dehydrated P_{Osm}) = (thirst TBW) X (thirst P_{Osm})

(37.8 L) X (305 mOsm/kg) = (? L) X (295 mOsm/kg)

(11,525 mOsmoles/295 mOsm/kg) = 39.07 L

The subject would consume 1.27 L (39.07 L - 37.8 L) in reaching the thirst threshold. This represents a **30.2 %** replacement of the total deficit (1.27 L X 100/4.2 L). Approximately100 ml of this 1.27 L would be returned to the plasma (1.27/12) and would reduce its deficit to **11%** (490 ml - 100 ml or (390/3500ml).

Thus, heat acclimatization could be expected to improve cardiovascular stability by reducing the solute loss and, thereby, preserving some plasma volume (390 ml vs 750 ml deficits). Moreover, it should have a pronounced impact on rehydration (**30.2% vs 1.7%**).

EXAMPLE 7
HYPOTONIC WATER DEFICIT IN THE HYPOHYDRATED, HEAT ACCLIMATIZED STATE

If the **same** subject began work, slightly **hypohydrated** at the thirst threshold, at a plasma osmolality of 295 mOsm/kg , he would have a TBW of 39.9 L (2.1 L deficit).

SOLUTE DEFICIT:

His total solute content is 11,760 mOsmoles (295 mOsm/kg X 39.9 L). His solute loss is equivalent to the sweat solute concentration 56 mOsm/kg X sweat volume (4.2L) = 235 mOsmoles. The salt-depleted solute content is 11,525 mOsmoles.

DEHYDRATION:

After losing a 4.2 L volume of sweat (39.9 L - 4.2 L = 35.7 L), the salt-depleted plasma osmolality would be 323 mOsm/kg (11,525 mOsmoles/35.7). The plasma deficit is equivalent to

0.84 L saline (235 /280 X 1000 of isotonic saline) of which the plasma contributes 1/4 = 210 ml. The pure water deficit equals 5460 ml (3360 ml [4200 ml - 840ml] + 2100 ml). The plasma contributes 665 ml (5460 ml/12= 455 ml + 210 ml). Thus, without drinking there would be a **19 % deficit** (665 ml X100/3500 ml) in plasma volume.

REHYDRATION:

If the subjects drank until the thirst threshold was reached, then:

$$(\text{dehydrated TBW}) \times (\text{dehydrated } P_{Osm}) = (\text{thirst TBW}) \times (\text{thirst } P_{Osm})$$

$$(35.7 \text{ L}) \times (323 \text{ mOsm/kg}) = (? \text{ L}) \times (295 \text{ mOsm/kg})$$

$$(11{,}531 \text{ mOsmoles}/295 \text{ mOsm/kg}) = 39.09 \text{ L}$$

The subject would consume 3.39 L (39.09 L -35.7 L) in returning to the thirst threshold. This represents an 81% replacement of the dehydration deficit (4.2 L) or a 54% replacement of the total deficit (6.3 L). **This again would be an important consideration for studies where the initial hydration status of the subjects were not known for the resultant rehydration value could be 54 or 81% rehydration of the experimental body weight change.** Approximately 282 ml of this would be returned to the plasma (3390 ml/12) and would reduce (668 ml- 282 ml) its' deficit to 386 ml. Thus, with drinking there would be an **11%** deficit in plasma volume (386 ml X 100/3500 ml).

These examples are summarized in Table 1 and indicate the profound impact of the initial physiological state as well as the type of dehydration on the expected rehydration.

TABLE 1

EFFECT OF PURE WATER LOSS, HYPOTONIC SWEAT LOSS AND HEAT ACCLIMATION ON THIRST AND REHYDRATION

Condition/ Example	Water Loss (L)/ % BW loss	Salt Loss (mOsm or mEq)	PV Loss (ml)/ ECF loss	%PV	P_{Osm} (mOsm)	% Re-hydration Estimated	Incidence
Voluntary dehydration euhydrated (Example 2)	4.2 L 6.0%	---	350 ml 1.4 L	-10%	311	50% 2.1 L	~3 days work cold/altitude
Shock/ Involuntary dehydration (Example 3)	7.4 L / 10.6%	---	616 ml 2.46 L	-18 %	350	---	Life raft/ confinement/ 5 days
Voluntary dehydration hypohydrated (Example 4)	6.3 L 9.0%	---	525 ml 2.1 L	-15%	330	66.7% 4.2 L	~4 days cold/altitude
Voluntary dehydration non-acclimated euhydrated (Example 5)	4.2 L 6.0%	588/ 294	700 ml 2.8 L	-20%	295.6	1.7% 70 ml	~4 hrs work heat
Voluntary dehydration acclimated euhydrated (Example 6)	4.2 L 6.0%	235/ 118	490 ml 1.75 L	-14%	305	30.2% 1.2 L	~4 hrs work heat
Voluntary dehydration acclimated hypohydrated (Example 7)	6.3 L 9.0%	235/ 118	668 ml 2.45 L	-19%	323	54% 3.39 L	~4 hrs work heat

The evaporative loss by a non-sweating man is comprised of the respiratory water loss and the insensible perspiration and is called the insensible water loss (29). It is not really possible to give a firm figure for either the respiratory water loss or for the insensible perspiration, because the lower the atmospheric water-vapor pressure, the greater the loss. Although the temperature and humidity of the expired air does not vary greatly (41), the increased water content (90% saturated; 12,36) relative to the inspired air represents an inevitable loss. Under normal conditions, respiratory water loss is about 200 ml per day but may be around 350 ml per day for men working in a dry climate and approach 1500 ml per day for men working at altitude in cold air (29). The insensible perspiration may be as low as 500 ml in a moist climate. It is clear from these examples that the desication producing a relatively pure water loss would be a slow process. For example, even at minimum water losses per day (1500 ml /24 h), it would take nearly 5 days to reproduce the situation in Example 2 (Table 1). This does not fit most military scenarios except abandonment in a liferaft or some involuntary confinement. Note the large increase in plasma osmolality or sodium (170 mEq/L) in this case and the enormous loss of fluid necessary to produce an 18% deficit in plasma volume. This is why shock from primary water depletion is relatively rare.

A pure water deficit producing a 6% loss in body weight (Table 1, Example 2) primarily through non-sweating means would probably have to occur through work in the cold at altitude. The large respiratory water loss (~1500 ml/day) would make this another unlikely military scenario. Even more unlikely, is the 6% loss in body weight superimposed upon a preexisting deficit (-3%) at the thirst threshold (9%, total; Example 4). Even if these examples overestimate the times required to produce this form of primary water depletion, they serve to illustrate the highly unlikely prospect of ever being militarily relevant.

The first hypotonic sweat losses calculated (Example 5) for non-acclimatized individuals are striking for several reasons. First, it takes a relatively short time to produce a severe loss in plasma volume (-20%, 4h) versus a similar deficit via pure water routes (-18%, 5days, Example 3). The calculated values are at equilibrium concentrations and plasma osmolality (and therefore, thirst) would be greater before the extracellular water debt were paid by intracellular losses. This indicates why thirst and rehydration experiments should not be started until the equilibrium state has been achieved. Second, the equilibrium plasma osmolality does not reflect the volume loss because of the concurrent salt losses. the pure water loss is absorbed just in reaching the thirst threshold. In these conditions, the only inclination to drink at equilibrium times would be due to volume-depletion signals. Third, the percent change in the extracellular fluid volume (2.8 L X 100/14 L) equals the percent change in plasma volume (-20%). Finally, this model assumes no gain in solute from a prior meal. This strongly reinforces the concept of skipped meals in the etiology of this condition and further lends support for electrolyte replacement as soon as even one meal is missed.

The advantages conferred by heat acclimation on reducing electrolyte losses are seen (Example 6) if one assumes equivalent volume losses. In actuality, either the times to achieve a 4.2 L deficit would be shorter or the volumes lost would be greater. The 50% reduction in sweat sodium losses (294 vs 118 mEq/L) reduces the plasma volume deficit from severe to moderate levels and, at the same time improves the osmotic drive for thirst (70 vs 1270 ml). The impact of sweat sodium reduction is further appreciated when one estimates that a 9% body weight loss in the acclimatized state (Example 7) is roughly equivalent to a 6% loss in the non-acclimatized condition (Example 5).

THIRST AND METABOLISM: THE ENERGY DEPLETION MODEL

It is interesting to note that hypoglycemia stimulates many hormones including vasopressin in both rats (8) and in humans (9). According to Vokes (58) the mechanism is secondary to an intracellular glucopenia since a similar effect can be induced with 2-deoxyglucose (58,60). Hypoglycemia has recently been identified as a serious complication of heat stroke and, along with dehydration, it could play a significant role in heat stroke pathophysiology. In this regard, we have recently attempted to identify the cellular site or location where the physical effects of heat are translated into the physiological manifestations of heat strain (27). The underlying mechanisms (cellular site) as well as the theoretical rationale could share a common application with thirst research and are reviewed here.

A list of the hypothetical characteristics of such a site are compiled in TABLE 2.

TABLE 2
CELLULAR SITE OF HEAT STROKE INJURY:
HYPOTHETICAL CHARACTERISTICS

* Common feature of all cells - especially nerves and muscles
* Temperature sensitive
* Related to cell volume changes
* Functionally related to the acclimatization response
* Functionally related to tolerance and fatigue
* Ability to generate heat
* Potential for inducing irreversible change

The key factors in this list all relate in some way to the sodium pump, a change in membrane permeability to sodium, a stimulation of metabolism and especially glycolysis and a resultant energy drain upon the cell. For example, consider these factors in TABLE 3 which tend to increase intracellular sodium and to drive the sodium pump in a hyperthermic person.

TABLE 3
FACTORS WHICH INCREASE SODIUM PERMEABILITY AND ENERGY DEMAND

* Active transport hydrolyzes 1 ATP/3 Na ions translocated for 2 K ions
* Heat increases kinetic energy and ion diffusion
* Heat increases intracellular acidity and a Na-H exchange
* Heat storage results in hypohydration and increased (Na)
* Increased extracellular sodium increases sodium permeability
* Hypohydration increases basal metabolism
* Heat increases the neural stimulation frequency to maintain force
* Each molecule of ACh stimulates a 50,000 cation flux at the receptor
* Increased neural stimulation increases sodium flux
* Heat and exercise produce regional ischemia
* Regional ischemia induces regional acidosis and increased sodium flux
* A doubling of cellular Na results in an 8-fold increase in ATP hydrolysis

Thus, all of these factors which stimulate the influx of sodium into the cell will increase ATP utilization, heat production, lactate formation and produce an energy drain upon the cell. We have referred to this concept as the Energy Depletion Model of heat stroke pathophysiology (27). Therefore, if these mechanisms produces an intracellular glucopenia, this could account for part of the increased ADH release and thirst associated with hyperthermia and account for the generalized increase in hormone release. In this regard it is also interesting to note that Andersson (4) suggests that the "thirst" receptors are also sensitive to temperature and that local warming of the preoptic region will elicit drinking in the water-fed goat, whereas preoptic cooling will inhibit it. This is exactly the behavior we would expect from a sodium pump-mediated process. For example, membrane leakage of sodium and potassium ions and the resultant active transport may account for nearly half of the basal metabolism of the brain (6, 62). Hypothermia provides clinical protection from circulatory arrest by thermally restricting Na channels, delaying energy depletion, delaying potassium efflux and stabilizing the cell membrane (7).

If extracellular fluid osmolality decreases, water must enter cells and cellular volume increase; conversely, if extracellular fluid osmolality increases, due to the addition of solutes that penetrate cell membranes poorly, water must leave cells and cellular volume decreases. Thus, the basic physiological mechanisms that control the osmolality of the extracellular fluid affect cell volume. The maintenance of cellular volume also depends upon the energy metabolism of the cell (51). Tissues incubated in a medium similar to extracellular fluid maintained a normal volume while respiring but swelled when metabolism was inhibited (34). Swelling was associated not only with the uptake of water but of extracellular solutes as well (37). Thus, two factors can cause or contribute to an increase in cellular volume: a decrease in extracellular osmolality and/or a decrease in the energy metabolism of the cell. These two facts must be borne in mind when interpreting factors that elicit thirst or appear to inhibit it.

Water itself appears to cross cell membranes very rapidly. This process could be considerably slower in vivo than in vitro experiments would suggest. The gain in water and solute when metabolism is depressed is expected from a Gibbs-Donnan system with the presence of nonpermeant polyvalent macromolecules restricted to one side of the membrane (34). Calculations show that there is is an excess of osmotic pressure in that compartment contributed by the polyvalent macromolecule itself and its' associated counterions. Only if the excess osmotic pressure is counterbalanced by some additional solute restricted to the opposite compartment will a steady state be achieved. It is the active extrusion of sodium in metabolizing tissues which allows stabilization of cellular volume. Since this transport of sodium out of the cell takes place against an electrochemical gradient, work or active transport is required. The energy comes from the metabolism of the cell and any inhibition of metabolism will result in the accumulation of sodium

in cells as in the kidney (30, 34, 37), the liver (16, 24), skeletal muscle (28, 45), cardiac muscle (42) and brain (11, 18).

As discussed by MacKnight and Leaf(34), a central question confronting physiologist in the mid-1950's was not why did cell cells swell when thier metabolism was inhibited but was restated (35) as why didn't cells swell given their high content of intracellular proteins and other macromolecules exerting an osmotic pressure? As recognized by Leaf (30) and as explained by MacKnight (33) "So long as the rate at which a substance crossed the membrane from the extracellular fluid into the cell was equaled by the rate at which it was passed from the cell to the extracellular fluid, that substance in effect would be held in the extracellular compartment and could offset the intracellular swelling force. They postulated that the active extrusion of sodium from the cells allowed stabilization of cellular volume in metabolizing tissues". It follows from this that sodium is leaking into cells at all times and therefore accounting for a substantial amount of their basal metabolic rate (6, 54, 62, 63). It also follows that if the thirst receptor were a sodium receptor, then it **could interpret an increase in sodium concentration and leak rate as an increase in energy demand.** This would add tremendous significance to the observation that thirst can be induced by brain heating and inhibited by brain cooling. If this were true , it would lead to a further profound insight; i.e. **Thirst could be sensing energy demand and therefore, could be intimately related to metabolism and hunger!**

For example, in 1963 Gutman (20) injected hydrochlorothiazide an inhibitor of active Na transport and observed reduced drinking in response to a load of hypertonic saline in nephrectomized rats. Injections of ouabain had a similar effect (10, 21). Ouabain apparently inhibits ADH release (21). It was also very interesting to note that glycerol (3) and deuterium (D2O) (2) are two weaker inhibitors of Na-K ATPase. D2O had the same inhibitory effects when

used as the solvent for hypertonic saline in goats (31, 53). Infusions of glycerol (39, 40) were found to suppress dehydrative thirst and ADH secretion "much more effectively than corresponding glucose infusions". This could suggest that thirst is more easily attenuated by inhibiting the activity of the Sodium-Potassium ATPase than by raising the glucose levels within the cell.

For example, if sodium were leaking into the cell at a higher rate, there would be a greater turnover of available ATP producing more ADP and Pi to stimulate metabolism, possibly glycolysis in the vicinity of the cell membrane. Inhibiting the Na-K-ATPase would likely reduce this source of metabolic stimulation and ATP demand would fall and concentrations would increase. Thus, low thirst would correlate with low pump activity and higher energy (ATP) levels within the cell (high thirst would correlate with high rates of sodium entrance, high rates of ATP hydrolysis, lower ATP levels, higher ADP and Pi levels and stimulated glycolysis). In this model, high thirst correlates with high pump activity and lower steady-state ATP levels. If the cellular trigger for thirst were related to lower ATP levels (Energy Depletion), then this might explain the analogous condition of high ADH release (8,9) with either intracellular glucopenia or 2-dG. If glucose were either unavailable (glucopenia) or unable (2-dG) to fuel glycolysis, then steady-state ATP levels would fall (Energy Depletion), thereby stimulating ADH release and thirst. Depending upon the situation (glucose concentration, insulin etc.), elevated glucose levels might elevate the ATP levels and inhibit thirst but even higher levels might deplete ATP levels by producing excess hexose phosphates. This difficult concept is summarized in TABLE 4.

TABLE 4

HIGH THIRST/ADH RELEASE	LOW THIRST/ADH RELEASE
Increased metabolic demand	**Low/normal metabolic demand**
elevated pl Na/Increased Na "leaks", hyperthermia	Low pl Na, Low "leaks", cold
Increased pumping/ lower ATP levels/ Increased glycolysis/lactate	Decreased pumping/ elevated ATP levals/ levels/elevated glucose
Inhibited metabolism	**Inhibited Na-K-ATPase**
Intracellular glucopenia/2dG/ lower ATP levels	Ouabain/hydrochlorothiazide/ glycerol/deuterium/ elevated ATP levels
Reduced blood volume/flow/ substrate/oxygen availability	

Table 4 is striking for the fact that it provides convincing logic that thirst and ADH release can both be defined/regulated in terms of energy balance rather than the more common approach using water deficits and elevated osmolalities. This concept is relatively sophisticated and useful because it **unifies** a number of observations that on the surface are either unrelated or difficult to interpret with the existing model (Hyperosmolality). The table also provides an interesting perspective on the potential for unravelling physiological regulation by **stimulating metabolic demand** or by **reducing the substrate availability** fueling it. Selective inhibition studies then tend to identify key enzymes/regulators in the system or switching points. For example, reducing the activity of the pump enzymes with ouabain might make more ATP available for other uses such as muscular contractility. Furthemore, this model actually **predicts** that a reduction in blood volume/flow and attendant reductions in substrate availability/use will stimulate thirst. This

explains the apparently inappropriate thirst found in salt depletion which tends to confound the hyperosmolality model.

Other recent experiments (56) infused equally hyperosmotic solutions of sodium, sucrose, urea and glucose, intravenously. All solutions appeared to raise CSF osmolality **and** sodium concentrations but only saline and sucrose stimulated thirst. These results appear to question the specificity of the receptor for sodium but are compatible with centrally located osmoreceptors since urea and glucose do not cause cellular dehydration. These results, however, do not rule out the possibility that either glucose or urea are interfering with some biochemical event in the receptor-response pathway nor is it clear, if a proper equilibrium had been established, why they should raise CSF sodium in the first place. It is likely that this debate will continue.

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